Genetics and nutrition: introduction to the symposium on human genetic variation and nutrition[1-3]

Artemis P Simopoulos, MD

Introduction

In the spring of 1975 at the 59th Annual Meeting of the Federation of American Scientists for Experimental Biology in Atlantic City, NJ, the American Institute of Nutrition sponsored a symposium on interactions of nutritional and genetic factors. The symposium was co-chaired by Drs Lucille S Hurley and Charles R Scriver and was a landmark.

The year 1975 was a memorable year indeed because two other events took place that relate to the participants of the present symposium. The Asilomar Conference on Recombinant DNA Molecules was held on February 24–27, 1975 at the Asilomar Conference Center in Pacific Grove, CA, and its report was published on May 28, 1975 (1). I was then the executive secretary of the Division of Medical Sciences of the National Research Council of the National Academy of Sciences and served as the project director of the conference and its report.

In June 1975 the book *Genetic Screening, Programs, Principles, and Research* was published by the National Research Council of the National Academy of Sciences (2). The book was the work of the Committee for the Study of Inborn Errors of Metabolism. The committee was chaired by Dr Childs and I was the project director. Both Drs Holtzman and Scriver were members of the committee. Today, 11 years later, we are participating in a symposium on genetic variation and nutrition because precise understanding of the extent of genetic variation in human beings has been made possible by advances in recombinant DNA technology that followed the Asilomar conference. In 1988 nutrition research is poised at the threshold of its golden epoch because of advances in molecular biology and genetics, physiology, endocrinology, genetic epidemiology, as well as advances in clinical medicine, such as pediatrics, internal medicine, and obstetrics.

The new genetics

Human populations represent storehouses of genetic variability, greater than appreciated until recently. Advances in genetic studies have pinpointed significant variability in biochemical and immunologic characteristics for individuals that involve many enzymes, proteins, blood groups, HLA systems, etc. Human variability has been demonstrated by use of linkage, other family studies, somatic cell genetic hybridization studies, and molecular genetic studies.

Molecular genetics indicate that more extensive variability occurs at the DNA level. The importance of advances in molecular biology and their application to genetic diseases has revolutionized our concepts and has provided the impetus to use the new techniques to identify those specifically at risk for chronic degenerative diseases. Thus, by use of the tools of molecular genetics, which combine classical family genetic studies with the newest in recombinant DNA techniques, it is now possible to develop diagnostic tests for specific inherited diseases. These studies were used at first for the diagnosis of single gene defects. It is now possible to use this approach to detect an individual's susceptibility to diseases caused by multiple factors. Research advances have developed data pertaining to the diagnosis of genetic predisposition to three major multifactorial polygenic diseases: atherosclerosis, hypertension, and diabetes.

The advent of recombinant DNA technology has brought about a radical change, with the development of

[1] From the Division of Nutritional Sciences, International Life Sciences Institute Research Foundation, Washington, DC.

[2] Supported by funds from the Howard Heinz Endowment.

[3] Address reprint requests to AP Simopoulos, Director, Division of Nutritional Sciences, International Life Sciences Institute Research Foundation, 1126 Sixteenth Street, NW, Washington, DC 20036.

Received July 26, 1988.

Accepted for publication August 2, 1988.

restriction-fragment-length polymorphisms (RFLPs) by which the enormous natural variation occurring in the human genome at the rate of approximately one base change per 100 nucleotides can be identified. Individual differences are produced by the DNA sequence variation that exists throughout the genome. The DNA between two individuals varies every 200–500 base pairs. DNA sequence variation is more frequent in the DNA between genes because natural selection conserves sequences that regulate gene expression and code for proteins.

Further progress has been made through DNA amplification techniques. Segments of total human DNA can be artificially amplified to yield amounts of a nearly pure gene region that was previously attainable only by molecular cloning. The base sequence of amplified DNA segments can be determined directly by conventional methods. As a result specific mutations and polymorphisms of DNA sequences can be identified rapidly without the need to clone the gene.

The new molecular technology has major practical benefits for preventive medicine. In the near future the human genome will be completely mapped, more and better genetic methods of prevention will be developed, and the replacement of some defective genes will become possible.

Genetic polymorphism and susceptibility to disease

Common alleles (variants at a single locus) or polymorphisms form the basis of human diversity, including the ability to handle environmental challenge. Such alleles are likely to have increased in prevalence because of positive selection acting on variants that confer selective advantage in the heterozygous state. For example, the genetic polymorphisms that contribute to the common polygenic diseases, such as coronary heart disease, essential hypertension, and diabetes mellitus, almost certainly have a high prevalence in the population. Perhaps the variants that once conferred selective advantage for our hunter-gatherer ancestors by maintaining blood pressure and blood glucose and plasma cholesterol concentrations in a hostile environment now respond to overnutrition by predisposing to the major diseases that affect modern man. Thus, the differences between humans in traits such as skin color, height, intelligence, and blood pressure extend to the ability to handle environmental insults such as exposure to infectious agents and chemical carcinogens and excessive consumption of saturated fatty acids and cholesterol.

Though medical genetics grew up in close association with pediatrics (all four of us participating in this symposium are pediatricians), it is also relevant to many other branches of medicine. There are many diseases of adult life in which genetic variants are factors that play a part in determining individual susceptibility to a particular condition. In adult medicine it is increasingly obvious that many common conditions, such as coronary heart disease, hypertension, and diabetes mellitus, have important genetic components and that preventive medicine could be much more efficient if it could be directed toward special high-risk groups rather than toward the general population.

Genetics deals with variation. A fundamental aspect of the genetics approach to disease is an appreciation of human variation: its nature and extent, its origin and maintenance, its distribution in families and populations, its interaction with environment, and its consequences for normal development and homeostasis. This is discussed by Dr Childs in his paper entitled "Genetic Variation and Nutrition."

Advances in human biochemical genetics have produced data that suggest considerable biochemical variability within and between human populations. Therefore, the relevance of this genetic information for human nutrition is considerable. Variation in nutritional requirements and the interaction of certain nutrients with genetically determined biochemical and metabolic factors suggest different requirements for individuals. This variation (like sex differences) is inborn and needs to be differentiated from variations caused by the life cycle (growth, pregnancy, and old age).

The impact of genetic variation on nutritional advice will continue to expand as human genes are located on the chromosome map, nucleotide sequences are described, and regulation of the gene's expression is delineated. DNA polymorphisms in noncoding regions will be precisely described and that will allow mapping of predictors and the identification of DNA markers for disease development. Therefore, nutrition advice will be tailored to the individual's needs.

We have the results of countless nutritional surveys carried out throughout almost the entire world. However, scientists interested in the role of family factors will have a hard time finding anything useful because these factors are almost never considered in the questionnaires. The genetic point of view needs to be brought to the attention of epidemiologists. It is indeed paradoxical that so much controversy exists among epidemiologists at a time when advances in molecular biology have led to development of genetic markers that add support to the concept of atherosclerosis as a polygenic and clinically heterogeneous disorder. It has also been shown that environmental factors, such as diet, act on this genetic background for expression of a disease process.

Specific preventive therapy for the individual at risk (genetic medicine) is radically different from the concept of uniform risk in the universal population, the conventional public health approach. Dr Scriver discusses this topic in his paper entitled "Nutrient-gene Interactions. The Gene is Not the Disease and Vice Versa." Future research ought to lead to the development of diets that are modified according to individual needs. Both government agencies and industry have a critical role to play in product development and in the education of the public in this era of molecular genetics and its contribution to nutritional recommendations.

Public policy considerations

Genetic variation bears on the development of public health policy as well as on the delivery of health care at the individual level. When nutritional recommendations are made, genetic variability among individuals in the population will need to be taken into consideration. If the number of individuals affected by the genetic variation becomes important for policy setting, then benefit must be considered from the standpoint of both society and the individual. Dr Holtzman discusses this and other public policy issues in his paper entitled "Genetic Variation in Nutritional Requirements and Susceptibility to Disease: Policy Implications."

A joint interdisciplinary effort of geneticists and nutritionists is needed because we are developing exciting information and generating data on the genetics of susceptibility to obesity—a major public health problem—and genetic markers for atherosclerosis, hypertension, diabetes, and aging.

Our understanding of the genotypic contribution to determining nutritional requirements is in the process of being revolutionized by molecular biology. We can now define the gene at the ultimate quantal level—its specific constituent nucleotides. To continue in its role as an integrator of genomic and environmental processes, nutritional science must adjust its focus to include the microstructure of the genome. Our success in this regard will be reflected by our ultimate shedding of the statistical trappings required for the study of systems with high variance. Ultimately, we will be able to understand nutritional metabolism at levels of discrimination sufficient to permit individual dietary prescription.

This year, genetics have claimed a central focus not only at the Annual Meeting of The American Society for Clinical Nutrition but also in forthcoming annual meetings of the American Federation for Clinical Research, the American Society for Clinical Investigation, the American Pediatric Society, and the Society for Pediatric Research.

Genetics and nutrition are both on the threshold of their golden epoch. It is therefore most fitting that we begin with the integration of both in this symposium on human genetic variation and nutrition.

References

1. Berg P, Baltimore D, Brenner S, Roblin RO III, Singer MF. Summary statement of the Asilomar conference on recombinant DNA molecules. Proc Natl Acad Sci USA 1975;72:1981–4.
2. Committee for the Study of Inborn Errors of Metabolism, National Research Council. Genetic screening, programs, principles, and research. Washington, DC: National Academy Press, 1975.